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ORIGINAL ARTICLE

Clinical implications of an analysis of pharmacokinetics of crizotinib coadministered with dexamethasone in patients with non-small cell lung cancer

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Abstract

Purpose Dexamethasone is a systemic corticosteroid and a known cytochrome P450 (CYP)3A inducer. Crizotinib is a selective tyrosine kinase inhibitor of *ALK*, *ROS1*, and *MET* and a substrate of CYP3A. This post hoc analysis characterized the use of concomitant CYP3A inducers with crizotinib and estimated the effect of dexamethasone use on crizotinib pharmacokinetics at steady state.

Methods This analysis used data from four clinical studies (PROFILE 1001, 1005, 1007, and 1014) including 1690 patients with non-small cell lung cancer with *ALK* or *ROS1* rearrangements treated with crizotinib at 250 mg twice daily. Frequency and reasons for use of concomitant CYP3A inducers, including dexamethasone, with crizotinib were characterized. Multiple steady-state trough concentrations ($C_{trough,ss}$) of crizotinib were measured for each patient. A linear mixed-effects model was used for within-patient comparison of crizotinib $C_{trough,ss}$ between dosing of crizotinib alone and crizotinib coadministered with dexamethasone consecutively for ≥ 21 days.

Results Dexamethasone was the most commonly used CYP3A inducer (30.4%). A total of 15 patients had crizotinib $C_{trough,ss}$ for both crizotinib dosing with and without dexamethasone. The adjusted geometric mean ratio of crizotinib $C_{trough,ss}$ following coadministration with dexamethasone relative to crizotinib without dexamethasone, as a percentage, was 98.2% (90% confidence interval, 79.1–122.0%).

Conclusions Crizotinib plasma exposure following coadministration with dexamethasone was similar to that when crizotinib was administered without dexamethasone, indicating dexamethasone has no effect on crizotinib exposure or efficacy. Other CYP3A inducers with similar potency would likewise have no clinically relevant effect on crizotinib exposure.

Keywords Crizotinib · CYP3A inducers · Dexamethasone · Non-small cell lung cancer · Targeted therapy

Introduction

Lung cancer is the second most common cancer in the world and the leading cause of cancer-related deaths in both men and women [1]. Approximately 85–90% of lung cancers are characterized as non-small cell lung cancer (NSCLC), with adenocarcinoma histology accounting for the majority of NSCLC cases [2]. Over the last 15 years, research has led to identification of distinct molecular subtypes of NSCLC characterized by genomic abnormalities in oncogenes, resulting in oncogene addiction. These observations subsequently initiated the development and approval of targeted agents for the molecular subtypes, and thereby significantly changed the paradigm of NSCLC treatment. Chromosomal rearrangements of anaplastic lymphoma kinase (*ALK*) and c-ros oncogene one (*ROS1*) genes are two such examples and account for 3–7% and 1–2% of all NSCLC cases, respectively [3, 4]. Patients with NSCLC with rearrangements of *ALK* or *ROS1* genes are considered to have *ALK*-positive or *ROS1*-positive NSCLC and are generally younger patients with adenocarcinoma history and former light smokers or nonsmokers [5]. In the era of precision oncology, tyrosine kinase

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inhibitors (TKIs) directed against *ALK* rearrangements or *ROS1* fusions have been studied and used for individualized therapy, leading to remarkable responses in select patients with NSCLC [6].

Crizotinib is a first-in-class, multitargeted TKI with activity against *ALK* [7, 8], ROS1 [9, 10], Recepteur d'Origine Nantais (*RON*), and *MET* [11] receptor tyrosine kinases and their oncogenic variants (e.g., *MET* mutations and *ALK* or *ROS1* fusion proteins). Crizotinib 250 mg administered orally twice daily (BID) is currently approved in over 90 countries worldwide for the treatment of patients with *ALK*-positive or *ROS1*-positive advanced NSCLC [12, 13]. Data from four clinical trials—PROFILE 1001 (ClinicalTrials.gov identifier, NCT00585195), PROFILE 1005 (NCT00932451), PROFILE 1007 (NCT00932893), and PROFILE 1014 (NCT01154140) [14–18]—demonstrated the clinical benefit of crizotinib for the treatment of *ALK*-positive advanced NSCLC in previously treated or untreated patients, with PROFILE 1001 also showing clinical benefit in patients with *ROS1*-positive NSCLC [19]. These studies also demonstrated that crizotinib has a tolerable safety profile [20].

Crizotinib is a substrate and a time-dependent inhibitor of cytochrome P450 (CYP)3A, which contributes to inhibition of its own metabolism and elimination, thus resulting in nonlinear pharmacokinetics (PK) after multiple dosing [21, 22]. PF-06260182, the most abundant circulating metabolite of crizotinib (~27% of parent drug), is a three- to eight-foldless potent ALK TKI than crizotinib that is formed predominantly by CYP3A, with minor contributions from other CYPs, and exclusively metabolized by CYP3A. In a study of 15 healthy volunteers, coadministration of a single dose of crizotinib 250 mg with a strong CYP3A inducer (rifampin 600 mg once daily for 14 days) resulted in an 82% and 94% reduction of crizotinib and PF-06260182 exposures, respectively, as measured by the area under the concentration-time curve from time zero to infinity [23]. However, the effect of weak or moderate CYP3A induction on crizotinib exposure is not known. Currently, it is recommended in the Crizotinib Summary of Product Characteristics that the combination of moderate or strong CYP3A inducers with crizotinib should be avoided [13].

Dexamethasone is a potent corticosteroid that is a weak-to-moderate inducer of CYP3A. The induction potential of dexamethasone on CYP3A is dose-dependent and occurs after multiple dexamethasone doses [24–26]. In studies using human hepatocytes, dexamethasone induced CYP3A at concentrations ranging from 1 to 100 μM, with the greatest induction effect observed at the highest concentration level [24, 26]. In a study of 12 healthy adults, dexamethasone 8 mg administered orally BID for 5 days resulted in a 25.7% average increase in hepatic CYP3A4 activity as measured by the erythromycin breath test [27]. This study found high variability in the induction of hepatic CYP3A4 activity (–6 to 70%), with about one-third of individuals experiencing a moderate increase in CYP3A4 activity (49–70%) [27].

This post hoc analysis characterizes the concomitant CYP3A inducers used by patients with NSCLC who were treated with crizotinib from all PROFILE studies (1001, 1005, 1007, and 1014) and estimates the effect of the concomitant use of dexamethasone on the PK of crizotinib and PF-06260182 at steady state.

Materials and methods

Summary of clinical studies

This analysis included data from four clinical studies—PROFILE 1001, PROFILE 1005, PROFILE 1007, and PROFILE 1014. PROFILE 1001 is an ongoing multinational, single-arm, open-label, dose-escalation study designed to evaluate the safety, PK, pharmacodynamics, and antitumor activity of crizotinib in patients with advanced cancer, including a cohort of patients with *ALK*-positive advanced NSCLC. General information on the methodology of this study has been described elsewhere [14, 19]. PROFILE 1005 was a multinational, single-arm, open-label, phase II study that evaluated the efficacy and safety of crizotinib in patients with *ALK*-positive advanced NSCLC [15, 18]. PROFILE 1007 was a randomized, open-label, phase III study of crizotinib versus standard-of-care chemotherapy (pemetrexed or docetaxel) in previously treated patients with *ALK*-positive advanced NSCLC [16]. PROFILE 1014 was a randomized, open-label, phase III study of crizotinib versus pemetrexed/cisplatin or pemetrexed/carboplatin in previously untreated patients with *ALK*-positive advanced NSCLC [17]. A continuous oral dosing schedule of crizotinib at a starting dose of 250 mg BID was used in all studies, with a cycle duration of 28 days for PROFILE 1001 and 21 days for PROFILE 1005, 1007, and 1014. All patients provided written informed consent before enrollment. The institutional review board or independent ethics committee at each participating center approved the protocol, which complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws.

Frequency of CYP3A inducer use with crizotinib

Concomitant medication use among patients treated with crizotinib was recorded for each of the four clinical studies. In the PROFILE studies, concurrent use of strong CYP3A inhibitors (such as clarithromycin, itraconazole, and grapefruit), strong CYP3A inducers (such as carbamazepine, phenobarbital, rifampin, and St John's wort), and sensitive CYP3A substrates with a narrow therapeutic index (such as

aripiprazole, triazolam, ergotamine, and pimozide) was not allowed. Only medications intended for systemic use and administered while patients were actively receiving crizotinib treatment were included. All topical or locally acting medications were excluded. On the basis of the medication name and investigator-reported reason for use, each incidence of concomitant medication use was categorized by its mechanism of action or therapeutic indication class. Concomitant medications were classified as CYP3A inducers of all potencies (e.g., weak, moderate, or strong) as defined by the University of Washington Metabolism and Transport Drug Interaction Database [28]. The number and frequency (%) of crizotinib-treated patients using concomitant medications were computed and reported by class.

Analysis of dexamethasone use with crizotinib

Reasons for concomitant dexamethasone use with crizotinib, along with dates of use, were reported by investigators for each incidence of daily dexamethasone administration. The reasons for dexamethasone use were broadly categorized into nine classifications: treatment of brain or central nervous system (CNS) symptoms, prevention/treatment of emesis, respiratory symptoms, other edema, pain, other adverse events, unspecified prophylaxis, anti-inflammatory, and other unrelated or unknown reasons. Long-term concomitant use of dexamethasone was defined as at least 21 days of consecutive dexamethasone dosing during crizotinib treatment. Investigator-reported reasons and duration of use for dexamethasone were summarized descriptively.

Analysis of crizotinib PK with and without dexamethasone

Plasma concentrations of crizotinib and its metabolite (PF-06260182) were collected and analyzed by liquid chromatography–tandem mass spectrometry as previously described [23]. For each patient, steady-state trough concentrations ($C_{trough,ss}$) of crizotinib and PF-06260182 were measured after ≥14 days of consecutive crizotinib 250 mg BID dosing. Crizotinib or PF-06260182 $C_{trough,ss}$ collected before any dexamethasone dosing or ≥14 days after the last dexamethasone dose served as the crizotinib without dexamethasone reference. Crizotinib coadministered with dexamethasone as the comparator was defined as crizotinib or PF-06260182 $C_{trough,ss}$ collected when dexamethasone was coadministered for ≥21 days before a $C_{trough,ss}$ collection. Within-patient comparisons of crizotinib and PF-06260182 $C_{trough,ss}$ between crizotinib coadministered with dexamethasone and crizotinib without dexamethasone were used to evaluate the effect of dexamethasone use on crizotinib and PF-06260182 $C_{trough,ss}$ values.

Statistical analysis

A linear mixed-effects model was used, and the dexamethasone effect was estimated by adjusted least-squares means for crizotinib without dexamethasone (reference group) and crizotinib coadministered with dexamethasone (test group). The statistical analysis was conducted using the R function lme() from the nlme package (R, version 3.0.3, R Foundation for Statistical Computing, Vienna, Austria) for linear mixed-effects modeling. The effect of dexamethasone was evaluated by estimating the adjusted geometric mean ratios (test group/reference group) and associated 90% confidence intervals (CIs).

Results

CYP3A inducer/dexamethasone use in crizotinib-treated patients

Across the PROFILE 1001, 1005, 1007, and 1014 studies, a total of 1690 patients received crizotinib treatment, of whom 1637 (96.9%) also received at least one concomitant medication while on crizotinib. CYP3A inducers that were concomitantly used with crizotinib included dexamethasone, methylprednisolone, prednisone, phenytoin/fosphenytoin, ginkgo/ginseng, phenobarbital, carbamazepine, efavirenz, and ritonavir. Strong CYP3A inducers were not allowed in the PROFILE studies. Use of systemic corticosteroids accounted for 745 (44%) of all concomitant medication use and included dexamethasone, methylprednisolone, and prednisone. Dexamethasone use accounted for 30.4% ($n=514$) of all patients who were treated with crizotinib, while fewer patients received the other CYP3A inducer systemic corticosteroids (methylprednisolone, $n=128$ [7.6%]; prednisone, $n=122$ [7.2%]). All other CYP3A inducers were rarely used (<1%). The list of concomitant CYP3A inducer use is summarized in Table 1.

Dexamethasone was the most commonly used CYP3A inducer and systemic corticosteroid among patients treated with crizotinib in the PROFILE studies. The reported reasons for dexamethasone use and duration of dexamethasone use varied widely (Figs. 1, 2a, b). The most commonly reported reason for dexamethasone use was to treat brain or CNS symptoms (24.7%). Other commonly reported reasons included unspecified prophylaxis (19.3%), prevention or treatment of nausea or emesis (18.7%), and treatment of other adverse events (18.3%). Prophylactic dexamethasone use was not specified by the investigators and could have been used for other treatment modalities. All other reasons for dexamethasone use were reported at low frequencies (<10%).

Table 1 Crizotinib-treated patients on CYP3A inducers

CYP3A inducer, *n* (%)	PROFILE 1001 *ALK* positive (*n* = 119)	PROFILE 1001 *ROS1* positive (*n* = 53)	PROFILE 1005 (*n* = 1066)	PROFILE 1007 (*n* = 172)	PROFILE 1014 (*n* = 280)	All studies (*N* = 1690)
Dexamethasone	20 (16.8)	13 (24.5)	339 (31.8)	58 (33.7)	84 (30.0)	514 (30.4)
Methylprednisolone	4 (3.4)	2 (3.8)	86 (8.1)	19 (11.0)	17 (6.1)	128 (7.6)
Prednisone	11 (9.2)	8 (15.1)	87 (8.2)	16 (9.3)	0	122 (7.2)
Phenytoin/fosphenytoin	0	0	10 (0.9)	4 (2.3)	2 (0.7)	16 (0.9)
Ginkgo/ginseng	0	0	4 (0.4)	4 (2.3)	0	8 (0.5)
Phenobarbital	0	0	6 (0.6)	1 (0.6)	0	7 (0.4)
Carbamazepine	0	0	4 (0.4)	0	1 (0.4)	5 (0.3)
Efavirenz	0	0	2 (0.2)	0	0	2 (0.1)
Ritonavir	0	0	1 (0.1)	0	0	1 (0.1)

ALK anaplastic lymphoma kinase, *CYP3A* cytochrome P450 3A, *ROS1* c-ros oncogene 1

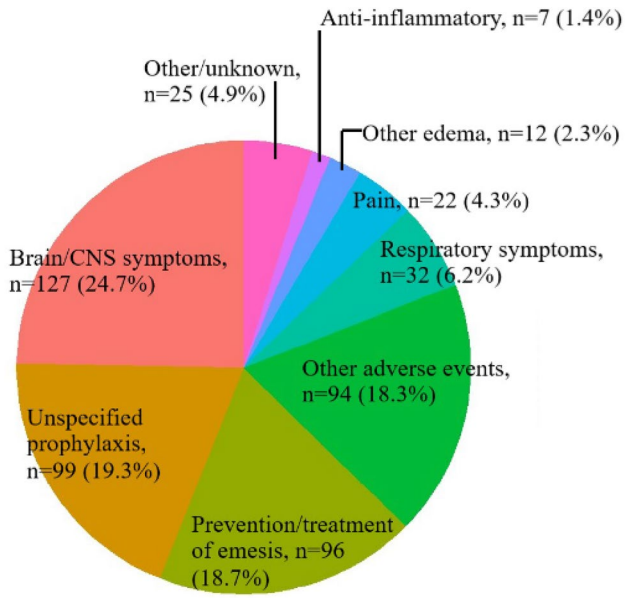

Fig. 1 Reasons for dexamethasone use. *CNS* central nervous system

Of all reported dexamethasone use, 69.2% (*n* = 342) included dates of dexamethasone use to allow for evaluation of duration of continuous dexamethasone use during crizotinib treatment. Median duration of dexamethasone use for treating respiratory symptoms, pain, other edema, and inflammation exceeded 21 days (25, 38.5, 35, and 332 days, respectively) (Fig. 2a). The median duration of dexamethasone use for the most commonly reported reason of treating brain or CNS symptoms was 20 days (range 1–420 days). Treatment of brain or CNS symptoms had the highest number of dexamethasone use events that were continuous for at least 21 days (Fig. 2b). Median durations of dexamethasone use for unspecified prophylaxis or prevention/treatment of nausea and emesis were relatively short (2 days [range 1–544 days] and 5 days [range 1–173 days], respectively).

Effect of dexamethasone on steady-state exposure of crizotinib and PF-06260182

Long-term dexamethasone use within the crizotinib analysis population is summarized in Table 2. Overall, 1059 patients from the 4 PROFILE studies had at least 1 $C_{trough,ss}$ of crizotinib or PF-06260182 in the analysis data set. Of these patients, 15 had crizotinib $C_{trough,ss}$ for both reference and test groups, this was the $C_{trough,ss}$ analysis population. Crizotinib $C_{trough,ss}$ values were similar when crizotinib was coadministered with or without dexamethasone (Fig. 3). The adjusted geometric mean crizotinib $C_{trough,ss}$ was 302.7 ng/mL for the crizotinib with dexamethasone group and 308.2 ng/mL for the crizotinib without dexamethasone group (Table 3). The adjusted geometric mean ratio of crizotinib $C_{trough,ss}$ following coadministration with dexamethasone relative to crizotinib without dexamethasone, as a percentage, was 98.2% (90% CI 79.1–122.0%), with the lower limit of the 90% CI just below the typical bioequivalence limits of 80–125%. The adjusted geometric mean PF-06260182 $C_{trough,ss}$ was 68.7 ng/mL for the crizotinib with dexamethasone group and 96.6 ng/mL for the crizotinib without dexamethasone group. The adjusted geometric mean ratio of PF-06260182 $C_{trough,ss}$ following coadministration with dexamethasone relative to crizotinib without dexamethasone, as a percentage, was 71.1% (90% CI 52.3–96.8%), indicating a statistically significant induction effect on the crizotinib metabolite, given that the upper limit of the 90% CI was <100%.

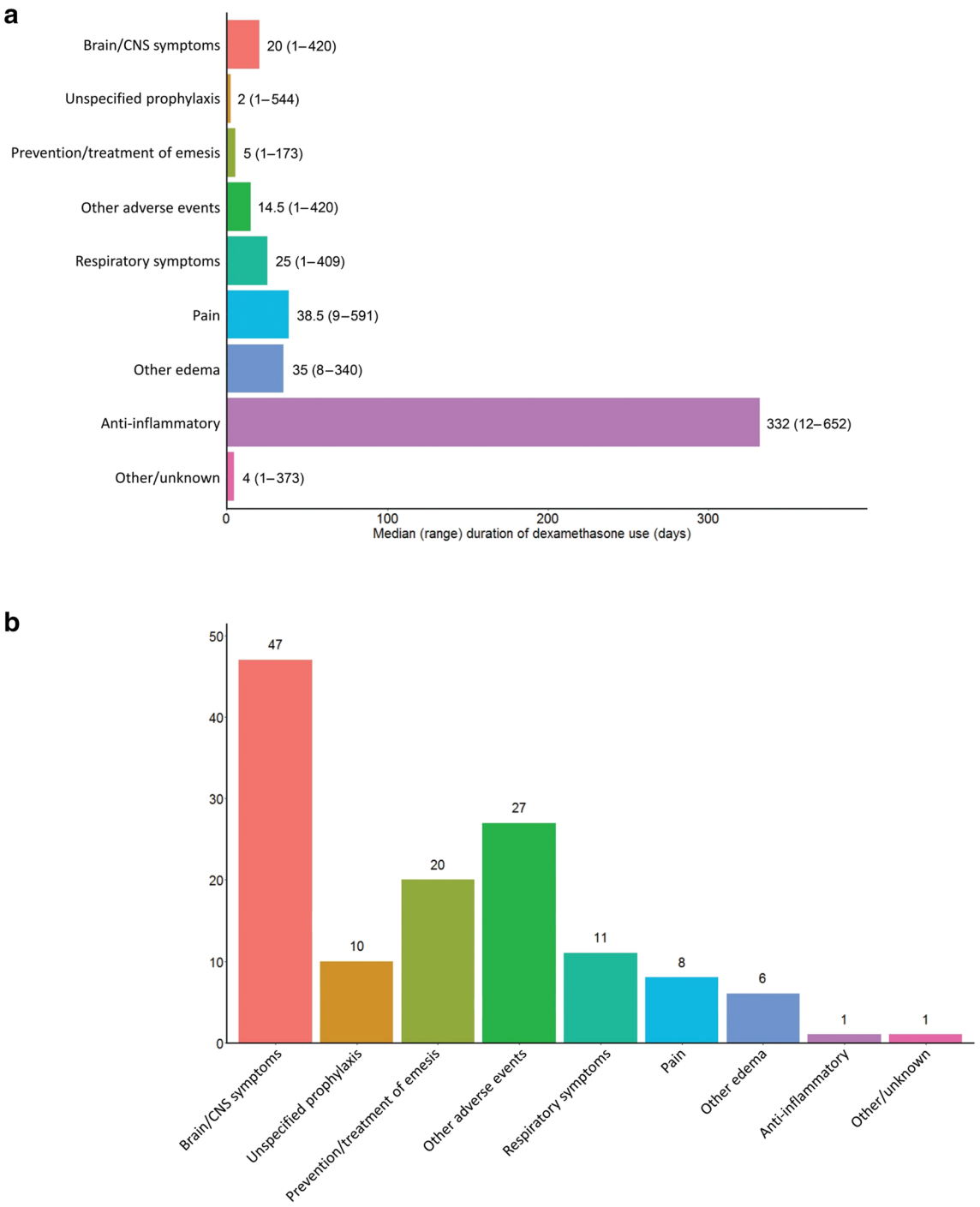

Fig. 2 Duration of dexamethasone use. **a** Median duration of dexamethasone use by reasons for use. Data are median (range) duration in days. **b** Number of instances of continuous dexamethasone use for ≥21 days by reasons for use. *CNS* central nervous system

Discussion

Brain and CNS metastases are generally associated with a poor prognosis, and if untreated, patients may experience profound neurologic symptoms [29]. Over the course of treatment, brain metastases occur in ~44% of patients with advanced NSCLC [30]. The frequency of brain metastases at diagnosis for patients with *ALK*-positive NSCLC was 23.8% [31], and the cumulative incidence of postdiagnosis brain metastases was reported to range from 30 to 60% [31–33]. There are many modalities to treat and control symptomatic brain metastases, including radiation therapy, chemotherapy,

Table 2 Analysis populations in PROFILE 1001, 1005, 1007, and 1014

Analysis population, *n*	PROFILE 1001	PROFILE 1005	PROFILE 1007	PROFILE 1014	Total
Crizotinib $C_{trough,ss}$	119	655	124	161	1059
≥21-day dexamethasone–crizotinib $C_{trough,ss}$[a]	3	9	2	1	15
≥21-day dexamethasone–PF-06260182 $C_{trough,ss}$[b]	0	9	2	1	12

$C_{trough,ss}$ steady-state trough concentration

[a]Patients had at least 21 days of combination treatment of crizotinib with dexamethasone and had at least 1 $C_{trough,ss}$ available for crizotinib for both reference and test groups

[b]Patients had at least 21 days of combination treatment of crizotinib with dexamethasone and had at least 1 $C_{trough,ss}$ available for PF-06260182 for both reference and test groups; PF-06260182 was not included in the analytic methods in PROFILE 1001

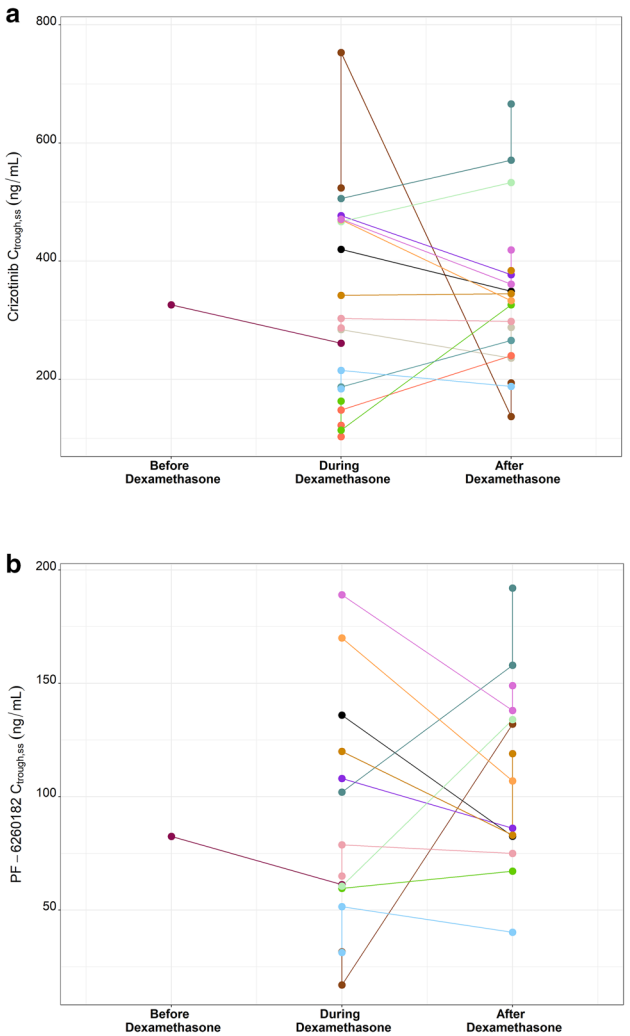

Fig. 3 $C_{trough,ss}$ values for **a** crizotinib ($n=15$) and **b** PF-06260182 ($n=12$). Individual $C_{trough,ss}$ observed is represented by distinct colors for each patient. Values of $C_{trough,ss}$ after dexamethasone are ≥14 days after the last dose date of dexamethasone. $C_{trough,ss}$ steady-state trough concentration

and other supportive care therapies, such as corticosteroids [34, 35]. The use of corticosteroids in the management of symptoms associated with cerebral edema in these patients, including patients with NSCLC with metastatic disease to the brain or CNS, has long been established [34–38]. Of the corticosteroids, dexamethasone is often selected for use because of its minimal mineralocorticoid effect and relatively long half-life compared with other drugs in its class [37]. A dexamethasone dose of 4–32 mg daily is recommended by the European Association of Neuro-Oncology for the treatment of patients with symptomatic brain metastatic disease [38].

This analysis showed a high frequency of dexamethasone use among crizotinib-treated patients with *ALK*-positive or ROS1-positive NSCLC, given that ~30% of reported concomitant medication use was dexamethasone. Moreover, the most commonly (25.8%) reported reason for the use of dexamethasone in these patients was for treatment of symptoms resulting from brain metastases. In this analysis, the median duration of dexamethasone treatment for brain/CNS symptoms was ~20 days. With long-term use of dexamethasone, drug–drug interactions are a potential concern because of the induction of the CYP3A enzyme.

In this analysis, no reduction in exposure to crizotinib with concurrent use of dexamethasone was observed; however, weak induction of CYP3A by dexamethasone was evidenced by reduced exposure to PF-06260182. Crizotinib is metabolized predominantly by CYP3A (~80% on the basis of an in vitro CYP phenotyping and the human mass balance study), while PF-06260182 is formed via oxidation mainly through CYP3A and is exclusively eliminated via CYP3A-mediated metabolism [21]. Thus, the elimination of PF-06260182 is predominantly more dependent on CYP3A metabolism than that for crizotinib, leading to a net decrease in PF-06260182 concentrations. The magnitude of decrease (29%) is not expected to be clinically meaningful, because PF-06260182 is only ~27% of parent drug in circulation and

Table 3 Adjusted geometric mean ratios of $C_{trough,ss}$ with and without dexamethasone

	Adjusted geometric mean $C_{trough,ss}$ (ng/mL)		Adjusted geometric mean ratio (%)	90% confidence interval
	Crizotinib with dexamethasone	Crizotinib without dexamethasone		
Crizotinib	302.7	308.2	98.2	79.1–122.0
PF-06260182	68.7	96.6	71.1	52.3–96.8

$C_{trough,ss}$ steady-state trough concentration

is a less-potent *ALK* inhibitor than the parent drug crizotinib. Dexamethasone coadministration with crizotinib treatment in patients with *ALK*-positive or ROS1-positive NSCLC had no effect on crizotinib exposure and, thus, was not expected to compromise crizotinib treatment efficacy. It was expected that other weak or moderate CYP3A inducers would likewise not have clinically relevant effects on crizotinib exposure and efficacy.

Many drug–drug interaction questions are answered through dedicated clinical studies with the drug of interest being dosed with a strong CYP enzyme inducer or inhibitor. However, the magnitude of effect of weak-to-moderate inducers and inhibitors and subsequent dosing recommendations are not as well characterized. Many of the small-molecule TKIs used in oncology are also substrates of metabolizing CYP enzymes. Therefore, it is important to gain better understanding and, ultimately, dosing recommendations for CYP substrate TKIs used concomitantly with inducers and inhibitors. The framework for this analysis can be applied when metabolizing CYP perpetrators are concomitantly used with drugs that are CYP substrates. Existing patient data from clinical studies offer an opportunity to characterize the landscape of concomitant medication use in the target patient population as well as to answer the question of potential PK effects as a result of these drug–drug interactions. Not only is this analysis more clinically relevant, but within-patient comparisons can reduce the bias caused by nonrandomized retrospective analyses. In this analysis, 1690 patients from 4 prospectively planned clinical studies of crizotinib (PROFILE studies) were included, with >1000 reported $C_{trough,ss}$ values. Of this large database, 15 patients of the $C_{trough,ss}$ analysis population met the criteria to evaluate the test comparison for the effect of dexamethasone on crizotinib exposure. These 15 patients had (1) at least 1 $C_{trough,ss}$ value measured before dexamethasone treatment or after dexamethasone treatment washout, and (2) at least 1 $C_{trough,ss}$ value measured when dexamethasone treatment was given for at least 21 days. Using a within-patient comparison (each patient serves as his or her own control), fewer patients are needed for a precise evaluation of the hypothesis. This was borne out by the reported narrow confidence limits (i.e., 90% CI 79.1–122.0%) for the geometric mean ratio of the crizotinib $C_{trough,ss}$ with and without concomitant dexamethasone. The methods used provide reasonable estimates of the effect with 15 patients, indicating that additional patients were not needed.

However, there are a few limitations to this approach. First, dexamethasone dosing information was not available from the PROFILE studies. Yet, given that the analysis population assessed chronic dexamethasone use over ≥21 days and that over one quarter of the incidences of dexamethasone use could be attributed to treating brain/CNS symptoms, the doses typically given for this indication (4–8 mg for mild symptoms and ≥16 mg for severe symptoms) [37] would also be doses where induction of CYP3A would be expected [27]. Moreover, the observed 29% decrease in the crizotinib metabolite PF-06260182 $C_{trough,ss}$, which is exclusively metabolized by CYP3A, indicates that the dexamethasone dose and duration of dosing in the analysis produced a weak CYP3A induction effect. Second, to validate the clinical relevance of the findings of this analysis, one should also evaluate crizotinib efficacy in patients who received concomitant dexamethasone because this would be a more direct approach for elucidating this question. However, the results of this type of evaluation would likely be confounded by disease status. In other words, patients with symptoms or complications such as brain metastases with poor prognoses are likely to be using dexamethasone. Indeed, worse outcomes were associated with baseline corticosteroid use of ≥10 mg equivalent of prednisone in a recent study that compared efficacy in patients with NSCLC treated with a single-agent programmed death-ligand 1 (PD-L1) antibody with or without baseline corticosteroid use [39]. Notably, this analysis was confounded by the correlation of baseline corticosteroid use with higher rates of history of brain metastases and Eastern Cooperative Oncology Group performance status ≥2, which lead to worse prognosis in patients with NSCLC. Therefore, our use of crizotinib exposure offers an indirect but unbiased evaluation of the effect of dexamethasone. Third, the $C_{trough,ss}$ metric, instead of the traditional metric of area under the concentration-time curve, was chosen as the PK end point for evaluating the effect of dexamethasone. Because of practical considerations in the phase II–III clinical trial settings, most patients enrolled in these clinical trials had limited PK sampling collections. Crizotinib $C_{trough,ss}$ was considered an appropriate surrogate of steady-state plasma exposure because the twice-daily dosing regimen of crizotinib, with a half-life of >40 h, resulted

in a high degree of drug accumulation (4.5 fold) at steady state.

In conclusion, dexamethasone was the most commonly used CYP3A inducer in patients with *ALK*-positive or *ROS1*-positive NSCLC treated with crizotinib in the PROFILE studies. The most commonly reported reason for dexamethasone use was to treat symptoms of brain or CNS metastases or disease. Crizotinib plasma exposure, as measured by mean $C_{trough,ss}$, following coadministration with dexamethasone was similar to that when crizotinib was administered without dexamethasone, indicating dexamethasone has no effect on crizotinib exposure. It is expected that other CYP3A inducers with similar potency would likewise have no clinically relevant effect on crizotinib exposure. The framework for this analysis can be applied when weak or moderate CYP3A inducers are concomitantly used with drugs that are CYP3A substrates.

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Compliance with ethical standards

Conflict of interest S. Lin, D. J. Nickens, K. D. Wilner, and W. Tan are employees of Pfizer. M. Patel was an employee of Pfizer during development of the manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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